UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,333	11/14/2001	Larry Wayne Oberley	875.042US1	5690

21186 7590 06/18/2002

SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER
SCHULTZ, JAMES

ART UNIT	PAPER NUMBER
1635	6

DATE MAILED: 06/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/993,333	Applicant(s) OBERLEY ET AL.
	Examiner James D. Schultz	Art Unit 1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Drawings

The drawing of figure 1 is objected to because it contains a sequence with no sequence identifier, either in the drawing or description of the drawing. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and 2-19 which follow from it are drawn to "an oligonucleotide comprising an antisense nucleic acid sequence that specifically binds to an antioxidant enzyme start codon..." The language of the claim renders the exact target of the antisense nucleic acid indefinite, since the term "antioxidant enzyme", as most commonly read, is a protein, and thus does not have a

start codon. The start codon could be a part of the nucleic acid encoding said enzyme, and if this is the intended target, should be defined as such.

Claims 2 and 3 are directed to the oligo of claim 1 that binds to an antioxidant enzyme, wherein the nucleic acid is 20 nucleotides long, or is "phosphothiolated". There are two nucleic acid sequences that are presumed to be referenced in claim 1; the antisense oligo, and the target, which is presumably not an oligo. Although the claim identifies the nucleic acid of claim 1 which is an oligo and thus presumably refers to the antisense oligo, the broadest interpretation of the "antioxidant enzyme" of claim 1 could also embrace a nucleic acid enzyme ("ribozyme") oligo. This interpretation results in two oligonucleotides being present in claim 1. Thus, the reference of claims 2 and 3 to "the oligonucleotide of claim 1" is indefinite. Also, "phosphothiolated" is not an art recognized term. The examiner presumes the reference is to phosphorothiolation; applicant is required to clarify the meaning of this term.

Claims 6, 7, 18 and 19 are drawn to the oligonucleotide of claim 1 or a method of using said oligonucleotide, wherein the nucleic acid sequence is 90% or 100% identical to the nucleic acid encoding an antioxidant enzyme. Said nucleic acid sequence of claim 1 is defined as being antisense, and thus could never have 90% or 100%, or even 1% identity to the nucleic acid encoding the antioxidant enzyme, since antisense sequences are, by definition, complementary.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is also referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov). The following passage is particularly relevant.

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within a genus, one must describe a sufficient number of species to reflect the variation within the genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

The invention of the above claims is drawn to oligonucleotide antisense compounds, and methods of using said compounds to treat diseases, that target the start codon of nucleic acids encoding antioxidant enzymes, wherein the target enzyme can be any antioxidant enzyme, or manganese superoxide dismutase, copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase, or wherein the antisense compound varies in length and sequence identity (presumed here to refer to homology with other antisense

molecules targeting antioxidant enzymes), or wherein the treatment is administered to mammals, or humans having an antioxidant enzyme malfunction disorder, or wherein the method comprises pharmaceutical carriers and vehicles.

The specification as filed discloses the sequence for human manganese superoxide dismutase, and methods of using specific antisense oligos to inhibit said dismutase. The specification as filed does not disclose any antioxidant enzymes other than human manganese superoxide dismutase at SEQ ID 11, either by structure, function, description of activity or by sequence that might have the claimed activity. However, said claims are drawn broadly to encompass the genus of all antioxidant enzymes, or a said subset of antioxidant enzymes, or to human superoxide dismutase, which includes all orthologs, splice variants and alleles thereof. Written description is provided only for human superoxide dismutase, SEQ ID No. 11.

A person of skill in the art would not view the disclosure from the specification of one sequence of human superoxide dismutase as being representative of the broad genus of all possible antioxidant enzymes claimed, or representative of the genus of copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase, or representative of the genus of orthologs, splice variants and alleles of human manganese superoxide dismutase other than that identified at SEQ ID No. 11, and would thus conclude that applicant was not in possession of these genii as broadly contemplated.

Moreover, since one cannot envision any antioxidant enzyme besides that identified at SEQ ID No. 11, one could not envision any antisense sequences that would act on said antioxidant enzymes that lack written description, beyond those disclosed in the instant

specification which hybridize and inhibit the human superoxide dismutase encoded by SEQ ID No. 11. Lastly, since the skilled artisan is unable to envision the genus of antisense enzymes, and in the absence of information in the specification regarding whether an enzyme "malfunction" of claim 8 enhances, inhibits or eliminates antioxidant activity, one could not readily envision a method of using antisense oligos to treat an antioxidant enzyme malfunction disorder of said claim.

Claims 8, 9, and 11-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vivo* antisense-mediated inhibition of human superoxide dismutase in the treatment of tumors, does not reasonably provide enablement for said inhibition of any/all antioxidant enzymes, or to treat heart disease, arthritis, or neurodegenerative diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed compounds and methods of using said compounds in the treatment of diseases other than that disclosed in the specification, e.g. tumor-related diseases. Although the specification prophetically considers using the claimed constructs in methods of inhibition or treatment of diseases other than tumor-related diseases, such a disclosure would not be considered enabling since no guidance is provided as to how to treat said diseases using the compounds disclosed in the instant application. Since no disclosure is provided as to how to use the antisense compounds of the instant application in the treatment of said diseases, such a

disclosure amounts to an invitation for experimentation, since protocols must be developed for use of the compounds of the instant application in the treatment of non-tumor related diseases, or novel antisense molecules must be synthesized and tested. The efficacy of untested antisense-mediated treatment of these diseases is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment of diseases.

A recent (2002) article by Braasch et al. opens by emphasizing that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach, and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, "it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, "[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency" (Page 378). "[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page 379.

Braasch et al. discusses the non-specific toxicity effects of *in vivo* antisense administration; "even when active oligomers are discovered, the difference in oligonucleotide dose required to inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism" (Pg. 4503, para. 1 and 2). Branch affirms that "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis" (Page 50), while Tamm et al. states that "[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally" (page 493, right column).

Further, Branch reasons that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (Page 46, second column). Tamm et al. concludes by stating that until "the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach."

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from the treatment of one disease, to the treatment of a broader range of diseases including heart disease, arthritis, or a neurodegenerative disease, as exemplified in the references above.

Further, one skilled in the art would not accept on its face the examples given in the specification of the treatment of a tumor-related disease as being correlative or representative of the successful *in vivo* use of antisense compounds or treatment of any and/or all conditions or diseases, or heart disease, arthritis, or a neurodegenerative disease suspected of being associated with antioxidant expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Said claims are drawn very broadly to compounds and methods of treating or preventing any condition or disease suspected of being associated with antioxidant enzyme expression in humans. The quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with low toxicity and immunogenicity that are successfully delivered, and most importantly, that target sites in appropriate cells and /or tissues harboring antioxidant enzymes such that all harmful expression is inhibited, that healthy expression is permitted appropriately *in vivo,* and further, that treatment and/or preventive effects are provided for any and/or all diseases or conditions suspected of being associated with antioxidant enzyme expression *in vivo*. Since the specification fails to provide any guidance for the successful treatment or prevention of any and/or all diseases or conditions suspected of being

associated with antioxidant enzyme expression in humans, or their tissues or cells, and since determination of these factors for a particular target gene in an organism is highly unpredictable, one of ordinary skill in the art would be unable to practice the invention as presented in the specification without engaging in undue trial and error experimentation over the scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Gonzalez-Zulueta et al.

The invention of the above claims is drawn to oligonucleotide antisense compounds that target the start codon of nucleic acids encoding antioxidant enzymes, which may be phosphorothiolated, wherein the target enzyme can be any antioxidant enzyme, or manganese superoxide dismutase, copper and zinc superoxide dismutase, catalase, phospholipid glutathione peroxidase, or cytosolic glutathione peroxidase, or wherein the antisense compound ranges in length from about 18 to 26, or is about 20, and has sequence identity of 90% or 100% (presumed here to refer to homology with other antisense molecules targeting antioxidant enzymes).

Gonzalez-Zulueta et al. teach a phosphorothiolated antisense compound that targets the start codon of human manganese superoxide dismutase and is 19 nucleotides long.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Schultz whose telephone number is 703-308-9355. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

James D. Schultz
June 17, 2002